High-Risk CDI Medications

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Nebraska ASAP Pharmacy Coordinator

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Nebraska Antimicrobial Stewardship Assessment and Promotion Program

CDI Prevention

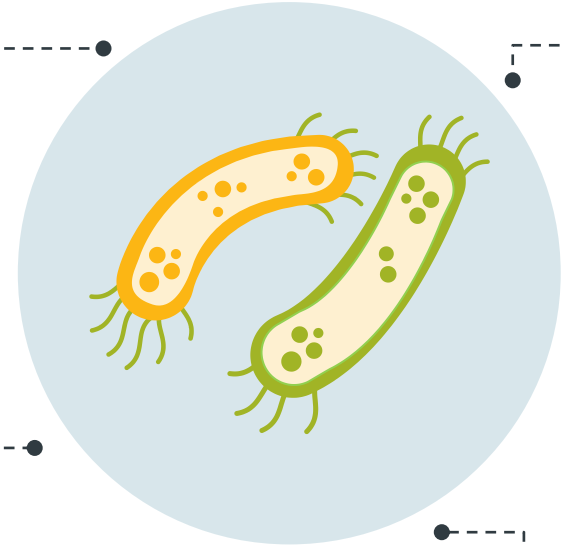
Contact Precautions	Implement appropriate infection control measures to prevent spread
Confirm CDI	Use appropriate testing strategies
Cleaning	Daily and terminal environmental cleaning with *C. difficile* sporicidal agent
Infrastructure	Education, auditing, contact precautions, cleaning, and feedback
Antibiotic Stewardship	Implement all 7 CDC Core Elements of ASP and focus on **minimizing high-risk antibiotics**

https://www.cdc.gov/hai/prevent/cdi-prevention-strategies.html

Objectives

01

Identify the antibiotics that have the highest risk of causing *Clostridioides difficile* infection



02

Describe the crucial role that antibiotic stewardship plays in preventing *Clostridioides difficile* infections

03

Recognize opportunities for preventing *Clostridioides difficile* infection by reducing the use of high-risk antibiotics in your facility

04

Summarize the role of gastric acid suppression on *Clostridioides difficile* infection risk

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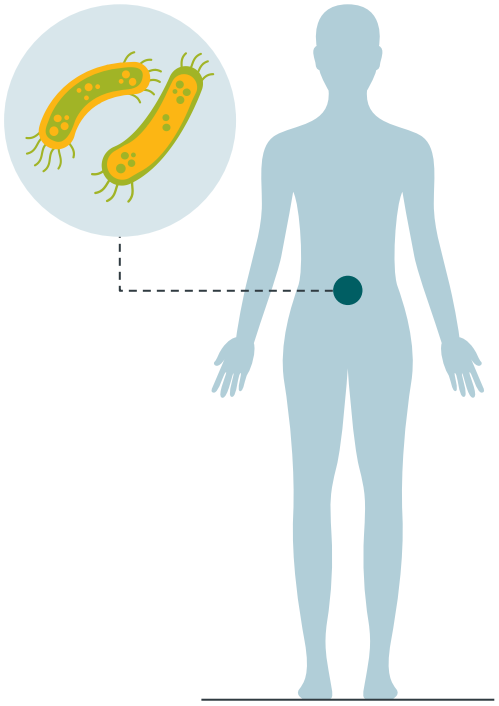
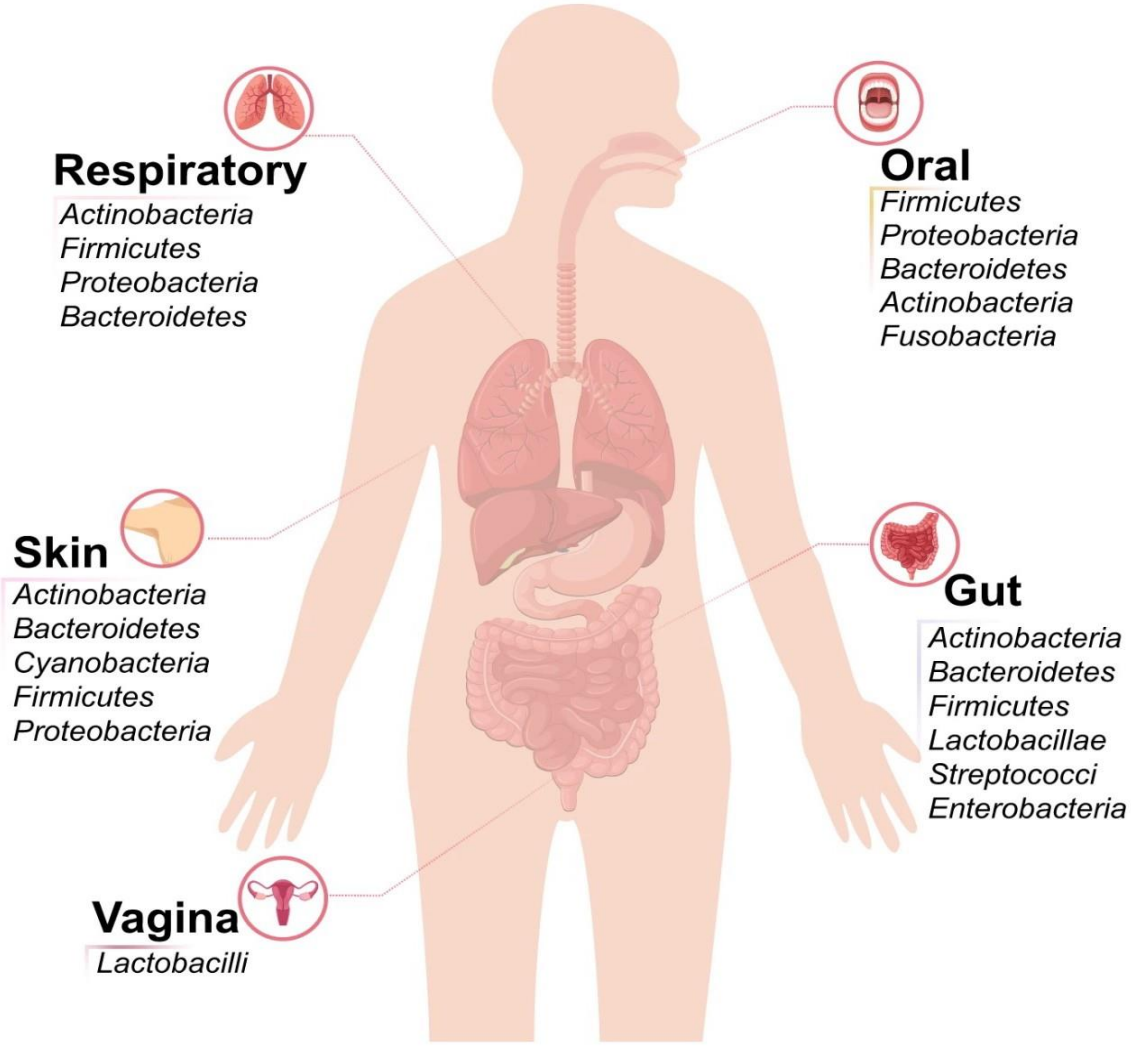


Objective 1

Identify the antibiotics that have the highest risk of causing *Clostridioides difficile* infection

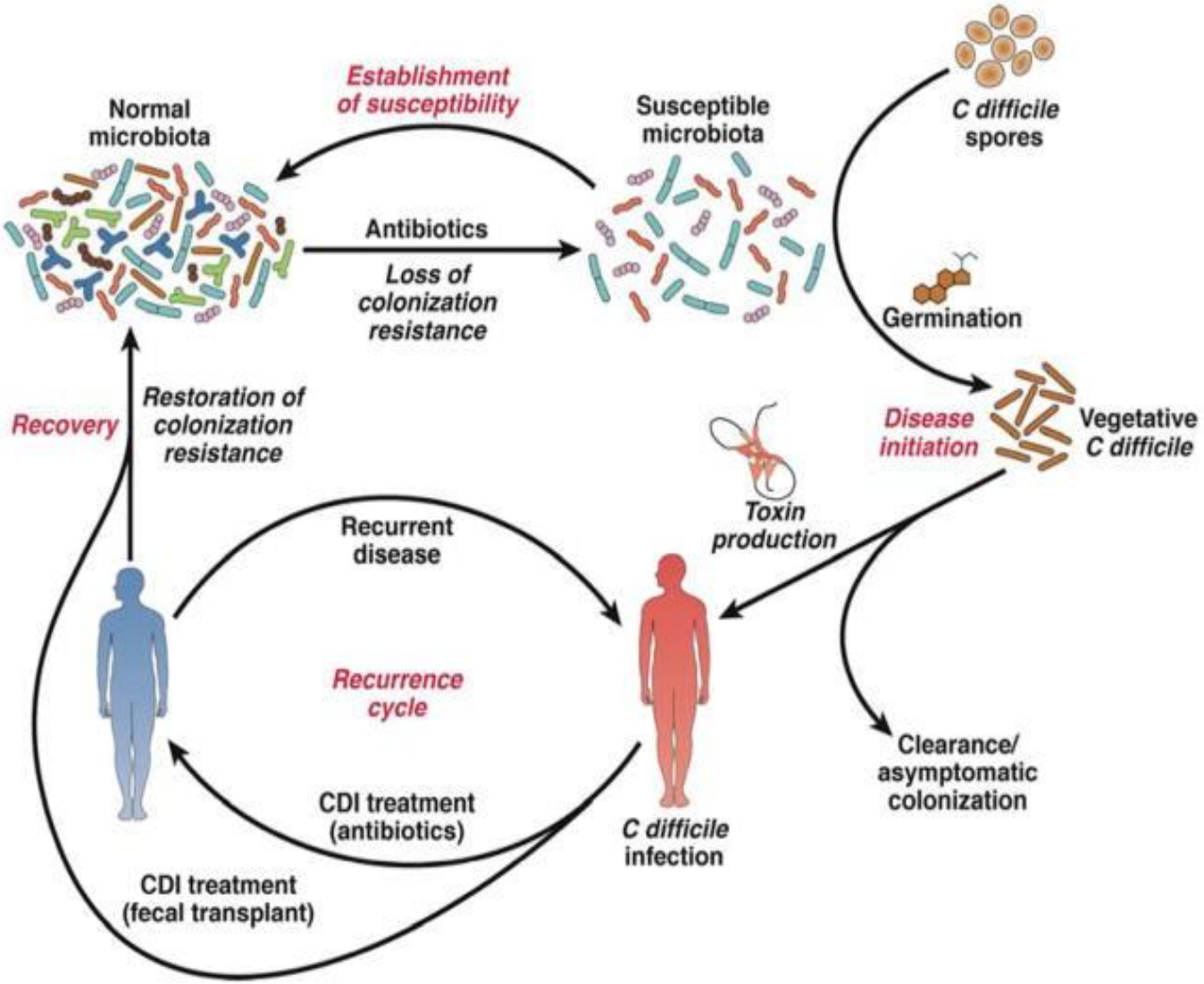
Antibiotics Impact the Human Microbiome



Human microbiota composition in different locations. Predominant bacterial genera in the oral cavity, respiratory tract, skin, gut, and vagina are highlighted

Hou, K., Wu, ZX., Chen, XY. *et al.* Microbiota in health and diseases. *Sig Transduct Target Ther* **7**, 135 (2022).

Antibiotics and CDI



Britton et al. *Gastroenterology*. 2014 May;146(6):1547–53.

Antibiotic Risk Stratification for CDI Risk

Low risk	Medium risk	High risk
Aminoglycosides	Co-amoxiclav	Second/third generation cephalosporins
Vancomycin	Macrolides	Clindamycin
Trimethoprim	Amoxicillin/ampicillin	Fluoroquinolones
Tetracyclines		
Piptazobactam		
Benzylpenicillin		

Monaghan et al. *Postgrad Med J*. 2009 Mar;85(1001):152-62.

High
- Clindamycin
- Flouroquinolones
- Cefepime
- Ceftriaxone
- Cefoxitin
- Cefdinir
- Meropenem
- Ertapenem

Medium
- Piperacillin-tazobactam
- Ampicillin-sulbactam
- Amoxicillin-clavulanate
- Cefuroxime
- Trimeth-Sulfa
- Azithromycin

Low
- Ampicillin
- Amoxicillin
- Cefazolin/Cephalexin

Very Low
- Doxycycline
- Oxacillin/Nafcillin
- Penicillin
- Aminoglycosides
- Aztreonam
- Colistin
- Daptomycin
- Linezolid
- Metronidazole
- Tigecycline
- Vancomycin

Nebraska Medicine Antibiogram

Table 1. Antibiotic Classes and Their Association with *Clostridium difficile* Infection.*

Class	Association with *C. difficile* Infection
Clindamycin	Very common
Ampicillin	Very common
Amoxicillin	Very common
Cephalosporins	Very common
Fluoroquinolones	Very common
Other penicillins	Somewhat common
Sulfonamides	Somewhat common
Trimethoprim	Somewhat common
Trimethoprim–sulfamethoxazole	Somewhat common
Macrolides	Somewhat common
Aminoglycosides	Uncommon
Bacitracin	Uncommon
Metronidazole	Uncommon
Teicoplanin	Uncommon
Rifampin	Uncommon
Chloramphenicol	Uncommon
Tetracyclines	Uncommon
Carbapenems	Uncommon
Daptomycin	Uncommon
Tigecycline	Uncommon

* Specific antibiotics are listed if their association with *C. difficile* infection differs from that of most other antibiotics in their class.

Leffler et al. *N Engl J Med.* 2015;372:1539-48.

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Highest Risk Antibiotics for CDI

Clindamycin[1]	Fluoroquinolones[1]	3rd/4th Generation Cephalosporins[1]	Carbapenems[2]
20.43 (8.50 – 49.09)	5.5 (4.26 – 7.11)	4.47 (1.6 – 12.5)	5.68 (2.12 – 15.23)
Risk of CDI Odds Ratio, (95% CI)	Risk of CDI Odds Ratio, (95% CI)	Risk of CDI Odds Ratio, (95% CI)	Risk of CDI Odds Ratio, (95% CI)

1. Deshpande A, Pasupuleti V, Thota P, Pant C, Rolston DD, Sferra TJ, Hernandez AV, Donskey CJ. Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. J Antimicrob Chemother. 2013 Sep;68(9):1951-61.

2. Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. Antimicrobial Agents and Chemotherapy 2013; 57(5): 2326-2332.

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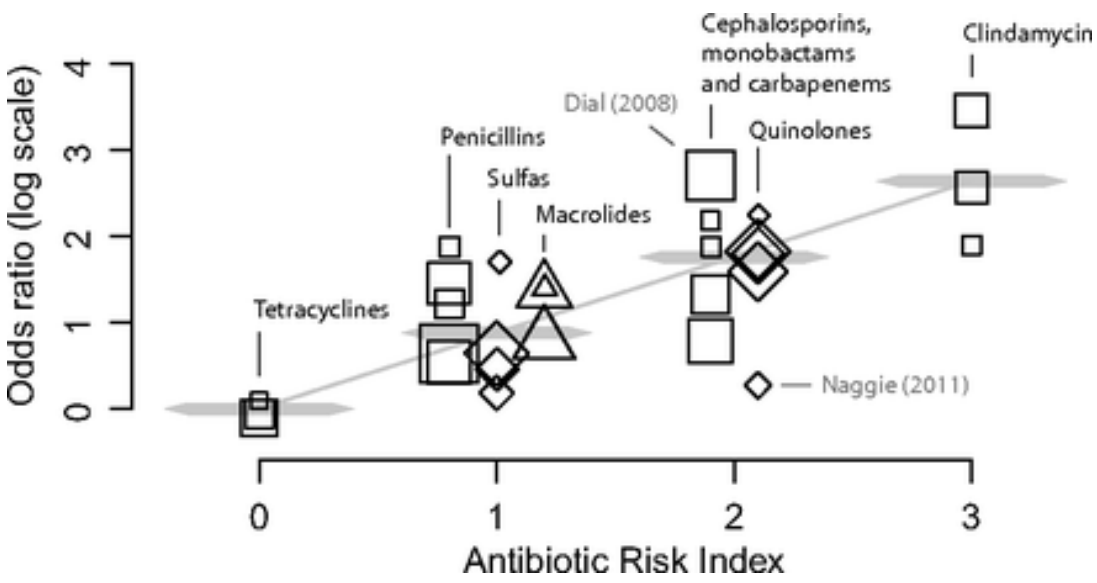
AAC
Journals.ASM.org

Meta-Analysis of Antibiotics and the Risk of Community-Associated *Clostridium difficile* Infection

Kevin A. Brown,[a] Nagham Khanafer,[b] Nick Daneman,[c] David N. Fisman[a]



High
- Clindamycin
- Flouroquinolones
- Cefepime
- Ceftriaxone
- Cefoxitin
- Cefdinir
- Meropenem
- Ertapenem

Medium
- Piperacillin-tazobactam
- Ampicillin-sulbactam
- Amoxicillin-clavulanate
- Cefuroxime
- Trimeth-Sulfa
- Azithromycin

Low
- Ampicillin
- Amoxicillin
- Cefazolin/Cephalexin

Very Low
- Doxycycline
- Oxacillin/Nafcillin
- Penicillin
- Aminoglycosides
- Aztreonam
- Colistin
- Daptomycin
- Linezolid
- Metronidazole
- Tigecycline
- Vancomycin

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Infection Control & Hospital Epidemiology (2019), **40**, 1229–1235
doi:10.1017/ice.2019.236

Original Article

Hospital-level high-risk antibiotic use in relation to hospital-associated *Clostridioides difficile* infections: Retrospective analysis of 2016–2017 data from US hospitals

Ying P. Tabak PhD[1], Arjun Srinivasan MD[2], Kalvin C. Yu MD[1], Stephen G. Kurtz MS[1], Vikas Gupta PharmD, BCPS[1], Steven Gelone PharmD[3], Patrick J. Scoble PharmD[3] and L. Clifford McDonald MD[2]

Table 1. Overall and Stratified Antibiotic and Other Medication Use

Variable	Overall Days of Therapy per 1,000 Days Present	
	Pooled Rate (n=171)	Median(1st, 3rd quartile)(n=171)
All risk antibiotics		
All risk antibiotics, range	N/A	178.1–835.4
All risk antibiotics	486.6	495.2 (424.5–565.8)
High-risk antibiotics		
Overall high-risk antibiotic, range	N/A	77.2–439.9
Overall high-risk antibiotics	230.6	241.2 (192.6–295.2)
Cephalosporins, 2nd/3rd/4th generation	110.5	110.7 (86.8–144.9)
Fluoroquinolones	72.8	76.6 (55.4–104.2)
Carbapenems	29.9	25.7 (15.7–38.2)
Lincosamides	17.5	17.0 (13.4–21.7)
Most frequently used medium- or low-risk antibiotic		
Piperacillin/tazobactam	81.7	81.8 (57.2–102.1)
Non-antibiotic		
Proton pump inhibitor	326.0	334.6 (265–371.9)

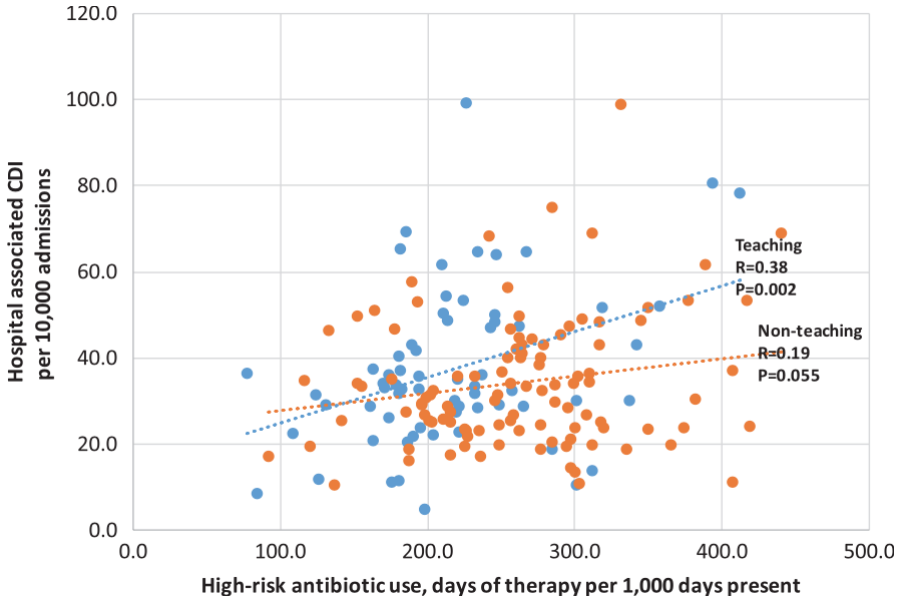
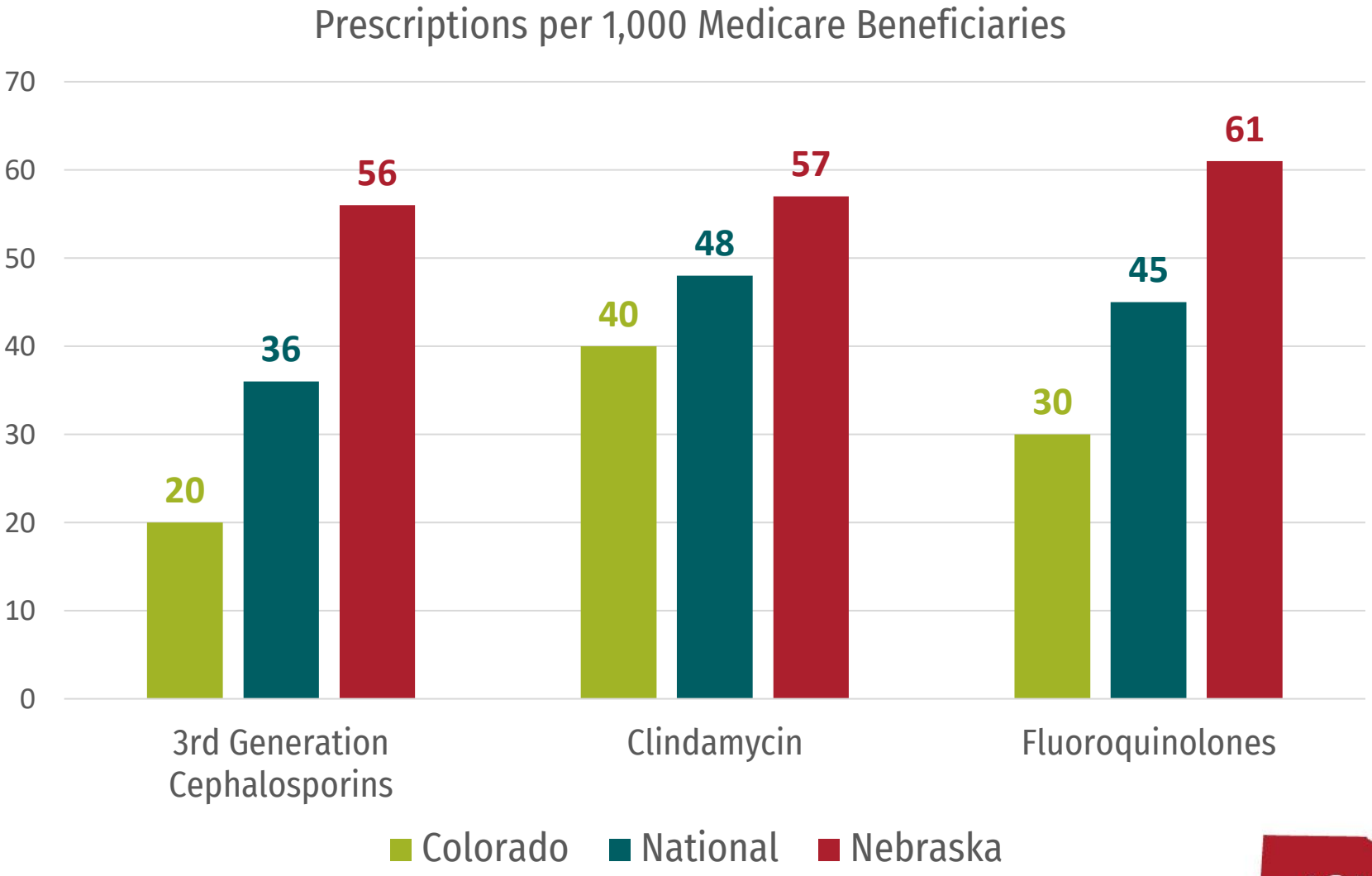


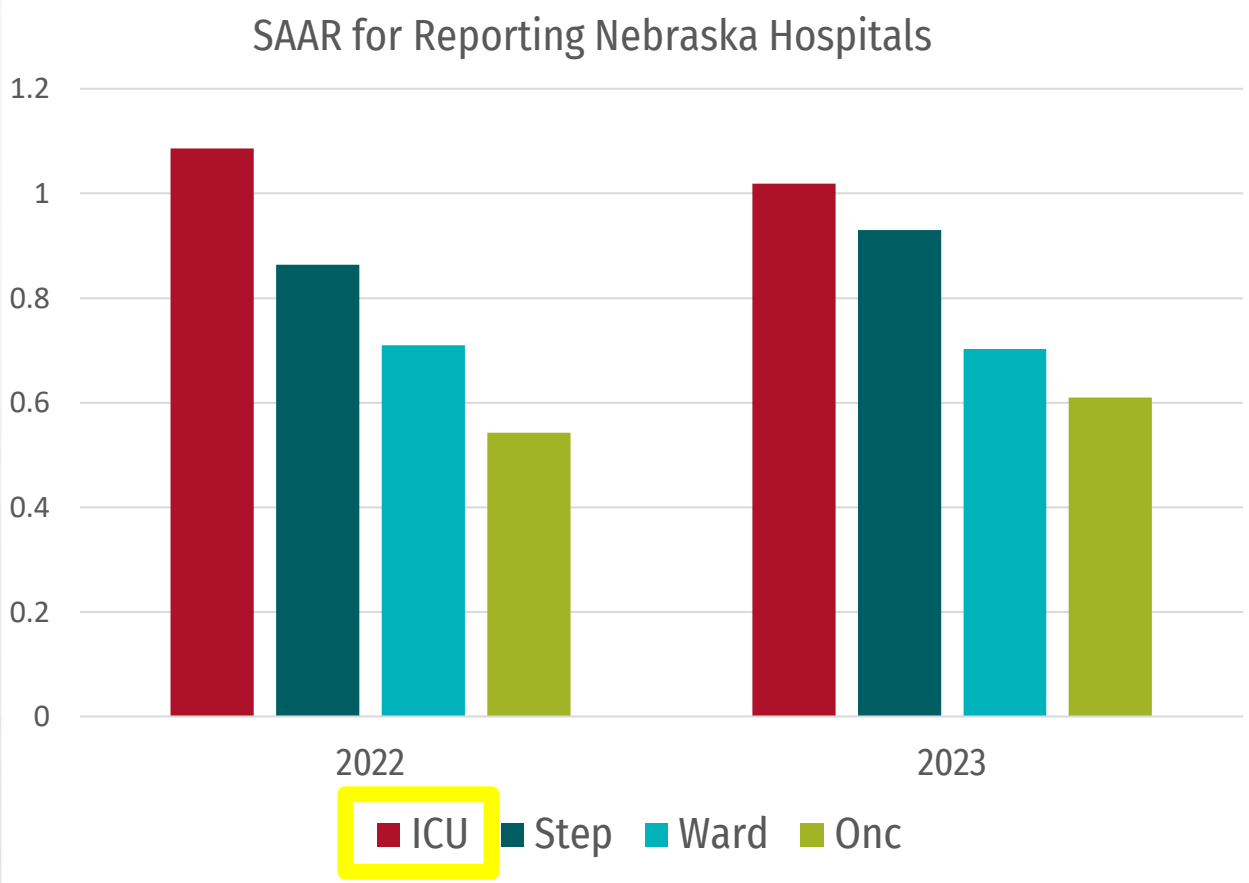
Fig. 2. Correlation of hospital high-risk antibiotic use and hospital-associated *Clostridioides difficile* infection rates stratified by hospital teaching status. The overall correlation coefficient for all 171 hospitals together was 0.22 ($P = .003$).

For every 100-day increase per 1000 patient days in high-risk antibiotic use, there was a 12% increase in HA-CDI (~4 additional cases)

Medicare Part D Antibiotic Prescribing, 2021



Nebraska Hospital Usage of High-Risk CDI Agents – NHSN AU Module

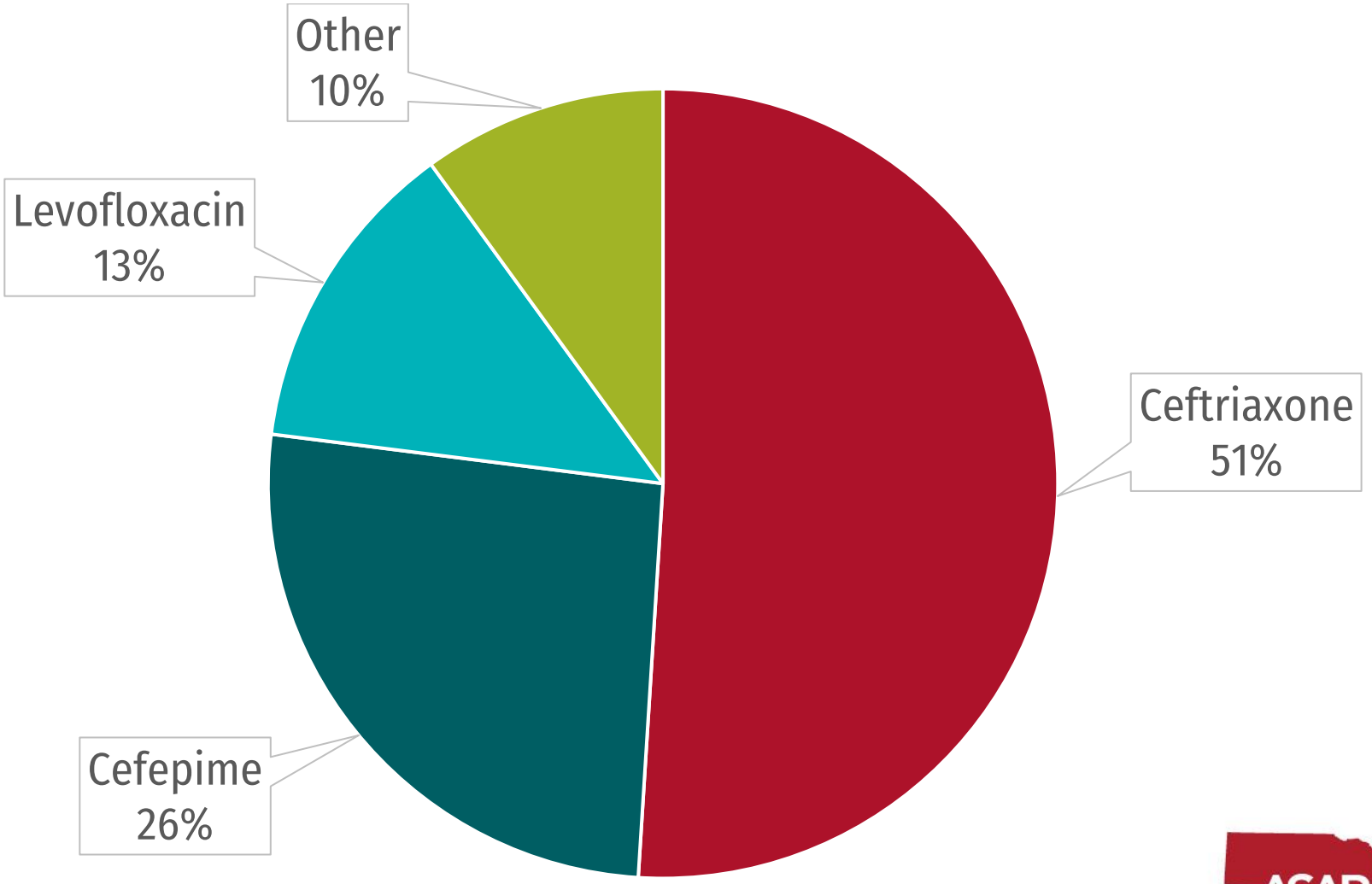


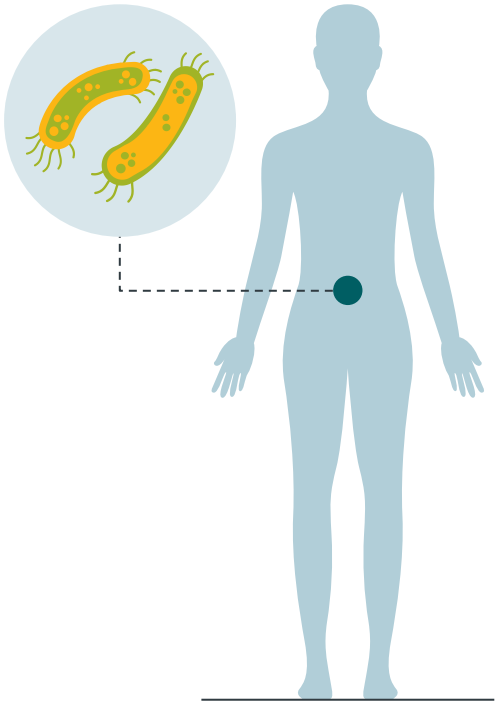
Antibiotics included in NHSN Calculation

- Cefdinir
- Cefepime
- Cefixime
- Cefpodoxime
- Ceftazidime
- Ceftriaxone
- Ciprofloxacin
- Clindamycin
- Levofloxacin
- Moxifloxacin

SAAR = Standardized Antibiotic Administration Ratio

Nebraska NHSN Antibiotic Use Data
High-Risk CDI Agents, 2022-2023





Objective 2

Describe the crucial role that antibiotic stewardship plays in preventing *Clostridioides difficile* infections

Antimicrobial Stewardship Interventions

Restrictive		
	Examples	• Prior authorization by ID PharmD or MD • Removal of agent from formulary
	Pros	• More direct control over use • Potentially larger impact
	Cons	• More labor-intensive • "Antibiotic police" culture
Non-Restrictive		
	Examples	• **Post-prescription review (prospective audit and feedback)** • Creation of or edits to existing guidelines • Provider education
	Pros	• Supportive culture • Educates providers to improve future decision-making
	Cons	• Less direct control over use • Potentially smaller impact compared to restrictive approaches

Wenzler et al. *Antibiotics (Basel).* 2015 Jun; 4(2): 198–215.

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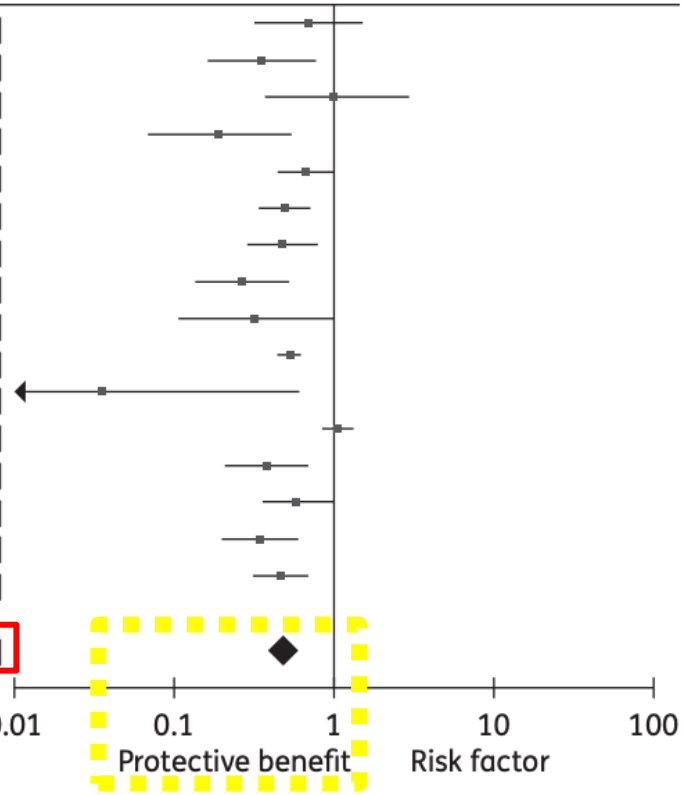
Effect of antibiotic stewardship programmes on *Clostridium difficile* incidence: a systematic review and meta-analysis

Leah M. Feazel[1], Ashish Malhotra[1,2], Eli N. Perencevich[1,2], Peter Kaboli[1,2], Daniel J. Diekema[1] and Marin L. Schweizer[1,2]*

Study of subgroup	log [Risk ratio]	SE	Weight	Risk ratio IV, Random, 95% CI
Elligson 2012	−0.37	0.393	5.0%	0.69 [0.32, 1.49]
Fowler 2007	−1.05	0.372	5.3%	0.35 [0.17, 0.73]
Frank 1997	0.029	0.522	3.6%	1.03 [0.37, 2.86]
Gulihar 2009	−1.65	0.522	3.6%	0.19 [0.07, 0.53]
Jones 1997	−0.4	0.205	8.1%	0.67 [0.45, 1.00]
Ludlam 1999	−0.721	0.177	8.7%	0.49 [0.34, 0.69]
Malani 2013	−0.755	0.257	7.2%	0.47 [0.28, 0.78]
Miller 2009	−1.341	0.341	5.8%	0.26 [0.13, 0.51]
O'Cornor 2004	−1.164	0.567	3.2%	0.31 [0.10, 0.95]
Price 2010	−0.661	0.082	10.1%	0.52 [0.44, 0.61]
Reinoso 2002	−3.372	1.438	0.7%	0.03 [0.00, 0.57]
Schön 2011	0.034	0.103	9.8%	1.03 [0.85, 1.27]
Starks 2008	−0.984	0.309	6.3%	0.37 [0.20, 0.68]
Stone 1998	−0.546	0.251	7.3%	0.58 [0.35, 0.95]
Talpaert 2011	−1.079	0.272	6.9%	0.34 [0.20, 0.58]
Thomas 2002	−0.78	0.19864	8.3%	0.46 [0.31, 0.68]
Total (95% CI)			100.0%	0.48 [0.38, 0.62]

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 61.27$, df = 15 ($P < 0.00001$); $I^2 = 76\%$

Test for overall effect: $Z = 5.94$ ($P < 0.00001$)



Feazel et al. *J Antimicrob Chemother*. 2014;69:1748-54.

Effect of antibiotic stewardship programmes on *Clostridium difficile* incidence: a systematic review and meta-analysis

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Table 2. Subset analyses

	No. of studies	Pooled risk ratio (95% CI)	Pooled effect *P* value
Overall	16	0.48 (0.38, 0.62)	<0.00001
Setting			
entire hospital	5	0.63 (0.42, 0.95)	0.03
geriatrics	6	0.44 (0.35, 0.56)	<0.00001
other[a]	5	0.42 (0.25, 0.71)	0.001
Intervention			
persuasive	5	0.49 (0.24, 1.01)	0.05
restrictive	8	0.46 (0.38, 0.56)	<0.00001
restrictive – entire hospitals	4	0.51 (0.44, 0.59)	<0.00001
removal from pharmacy	5	0.46 (0.37, 0.58)	<0.00001
prior approval	3	0.50 (0.36, 0.68)	<0.0001
post-prescription review	4	0.38 (0.88, 0.67)	0.0007

Take home point – you can focus on specific areas of your hospital and use whichever type of stewardship intervention strategy your team feels would best fit your hospital. All antibiotic stewardship efforts showed an improvement in C. diff rates!

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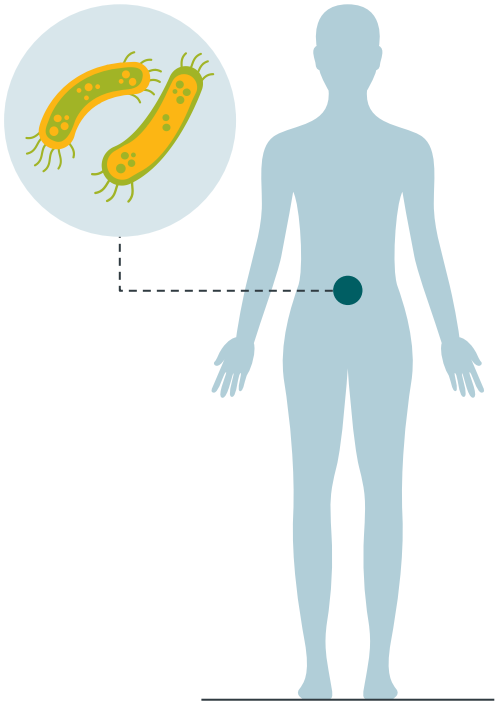
Feazel et al. *J Antimicrob Chemother*. 2014;69:1748-54.

Click here to complete an antibiotic stewardship assessment in your hospital:
[Antimicrobial Stewardship Assessments - ASAP (nebraskamed.com)]



Objective 3

Recognize opportunities for preventing *Clostridioides difficile* infection by reducing the use of high-risk antibiotics in your facility

Opportunities to Reduce High-Risk CDI Antibiotic Use

Image: Slidesgo.com

- Penicillin Allergic Patients
- Surgical Prophylaxis
- Community-Acquired Pneumonia

Penicillin Allergy Statistics

Penicillin is the most commonly reported drug allergy.[1]

of patients in the US report penicillin allergy.[1]

9 out of 10 reporting penicillin allergy are not truly allergic.[4]

80% of patients with IgE-mediated penicillin allergy lose the sensitivity after 10 years.[4]

Shenoy, ES, Evaluation and Management of Penicillin Allergy. JAMA, 2019

Consequences of Inaccurate

Penicillin Allergy Labels

Treatment failure

2nd line agents have inferior coverage

Adverse Drug Events

Clostridioides difficile infection
Increased drug-drug interactions
Medication side effects

Increased all-cause mortality

Antibiotic Resistance

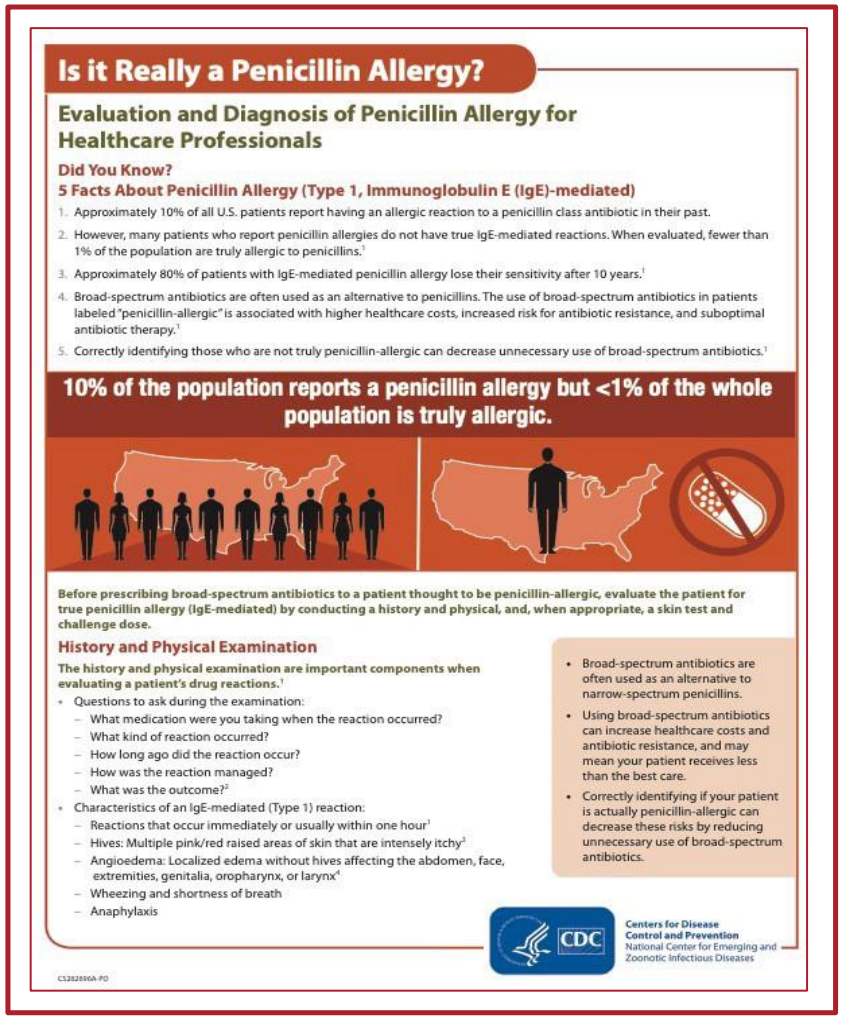
Increased development of Methicillin-Resistant *Staphylococcus aureus* and Vancomycin-Resistant *Enterococcus*

Surgical Site Infections

More common when alternative antibiotics are chosen

Samarakoon U et al. Ann Allergy Asthma Immunol. 2022 Dec 20;S1081- 1206(22)02006-3

CDC Urges ALL Healthcare Professionals to Evaluate Penicillin Allergies



Is it Really a Penicillin Allergy?

Evaluation and Diagnosis of Penicillin Allergy for Healthcare Professionals

Did You Know?

5 Facts About Penicillin Allergy (Type 1, Immunoglobulin E (IgE)-mediated)

1. Approximately 10% of all U.S. patients report having an allergic reaction to a penicillin class antibiotic in their past.
2. However, many patients who report penicillin allergies do not have true IgE-mediated reactions. When evaluated, fewer than 1% of the population are truly allergic to penicillins.[1]
3. Approximately 80% of patients with IgE-mediated penicillin allergy lose their sensitivity after 10 years.[1]
4. Broad-spectrum antibiotics are often used as an alternative to penicillins. The use of broad-spectrum antibiotics in patients labeled "penicillin-allergic" is associated with higher healthcare costs, increased risk for antibiotic resistance, and suboptimal antibiotic therapy.[1]
5. Correctly identifying those who are not truly penicillin-allergic can decrease unnecessary use of broad-spectrum antibiotics.[1]

10% of the population reports a penicillin allergy but <1% of the whole population is truly allergic.

Before prescribing broad-spectrum antibiotics to a patient thought to be penicillin-allergic, evaluate the patient for true penicillin allergy (IgE-mediated) by conducting a history and physical, and, when appropriate, a skin test and challenge dose.

History and Physical Examination

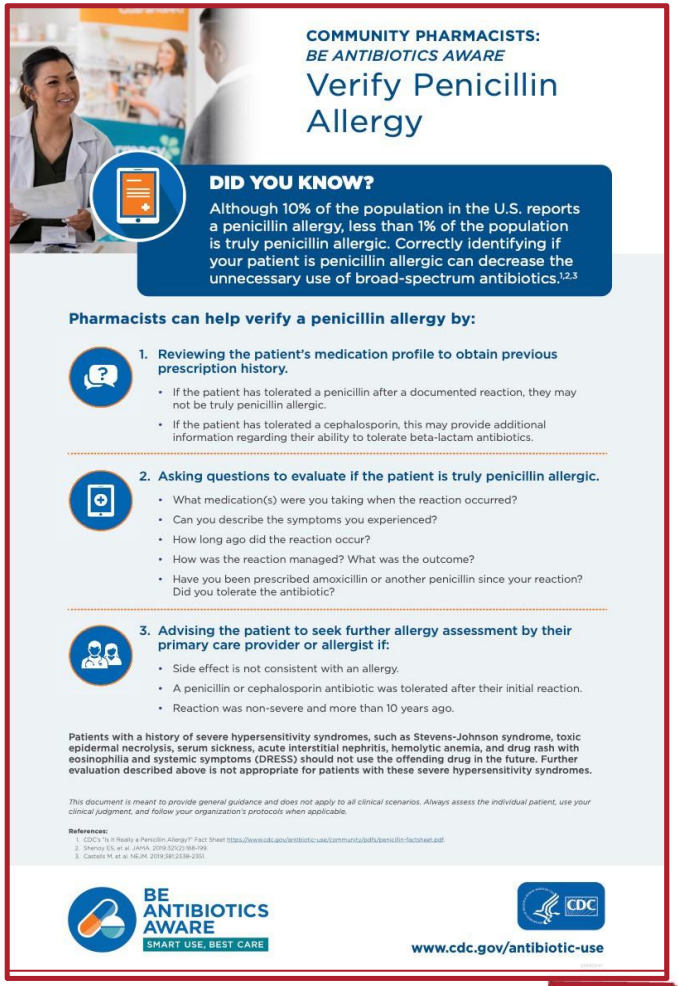
The history and physical examination are important components when evaluating a patient's drug reactions.[1]

- Questions to ask during the examination:
  - What medication were you taking when the reaction occurred?
  - What kind of reaction occurred?
  - How long ago did the reaction occur?
  - How was the reaction managed?
  - What was the outcome?[2]
- Characteristics of an IgE-mediated (Type 1) reaction:
  - Reactions that occur immediately or usually within one hour[1]
  - Hives: Multiple pink/red raised areas of skin that are intensely itchy[3]
  - Angioedema: Localized edema without hives affecting the abdomen, face, extremities, genitalia, oropharynx, or larynx[4]
  - Wheezing and shortness of breath
  - Anaphylaxis

- Broad-spectrum antibiotics are often used as an alternative to narrow-spectrum penicillins.
- Using broad-spectrum antibiotics can increase healthcare costs and antibiotic resistance, and may mean your patient receives less than the best care.
- Correctly identifying if your patient is actually penicillin-allergic can decrease these risks by reducing unnecessary use of broad-spectrum antibiotics.

CDC Centers for Disease Control and Prevention
National Center for Emerging and Zoonotic Infectious Diseases

CS282696A-PD



COMMUNITY PHARMACISTS:
BE ANTIBIOTICS AWARE

Verify Penicillin Allergy

DID YOU KNOW?

Although 10% of the population in the U.S. reports a penicillin allergy, less than 1% of the population is truly penicillin allergic. Correctly identifying if your patient is penicillin allergic can decrease the unnecessary use of broad-spectrum antibiotics.[1,2,3]

Pharmacists can help verify a penicillin allergy by:

1. **Reviewing the patient's medication profile to obtain previous prescription history.**
   - If the patient has tolerated a penicillin after a documented reaction, they may not be truly penicillin allergic.
   - If the patient has tolerated a cephalosporin, this may provide additional information regarding their ability to tolerate beta-lactam antibiotics.
2. **Asking questions to evaluate if the patient is truly penicillin allergic.**
   - What medication(s) were you taking when the reaction occurred?
   - Can you describe the symptoms you experienced?
   - How long ago did the reaction occur?
   - How was the reaction managed? What was the outcome?
   - Have you been prescribed amoxicillin or another penicillin since your reaction? Did you tolerate the antibiotic?
3. **Advising the patient to seek further allergy assessment by their primary care provider or allergist if:**
   - Side effect is not consistent with an allergy.
   - A penicillin or cephalosporin antibiotic was tolerated after their initial reaction.
   - Reaction was non-severe and more than 10 years ago.

Patients with a history of severe hypersensitivity syndromes, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, serum sickness, acute interstitial nephritis, hemolytic anemia, and drug rash with eosinophilia and systemic symptoms (DRESS) should not use the offending drug in the future. Further evaluation described above is not appropriate for patients with these severe hypersensitivity syndromes.

This document is meant to provide general guidance and does not apply to all clinical scenarios. Always assess the individual patient, use your clinical judgment, and follow your organization's protocols when applicable.

References:
1. CDC's "Is It Really a Penicillin Allergy?" Fact Sheet https://www.cdc.gov/antibiotic-use/community/pdfs/penicillin-factsheet.pdf
2. Shenoy ES, et al. JAMA. 2019;321(2):188-199.
3. Castells M, et al. NEJM. 2019;381:2338-2351.

BE ANTIBIOTICS AWARE
SMART USE, BEST CARE

CDC
www.cdc.gov/antibiotic-use

https://www.cdc.gov/antibiotic-use/clinicians/Penicillin-Allergy.html

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CDC Urges ALL Healthcare Professionals to Evaluate Penicillin Allergies

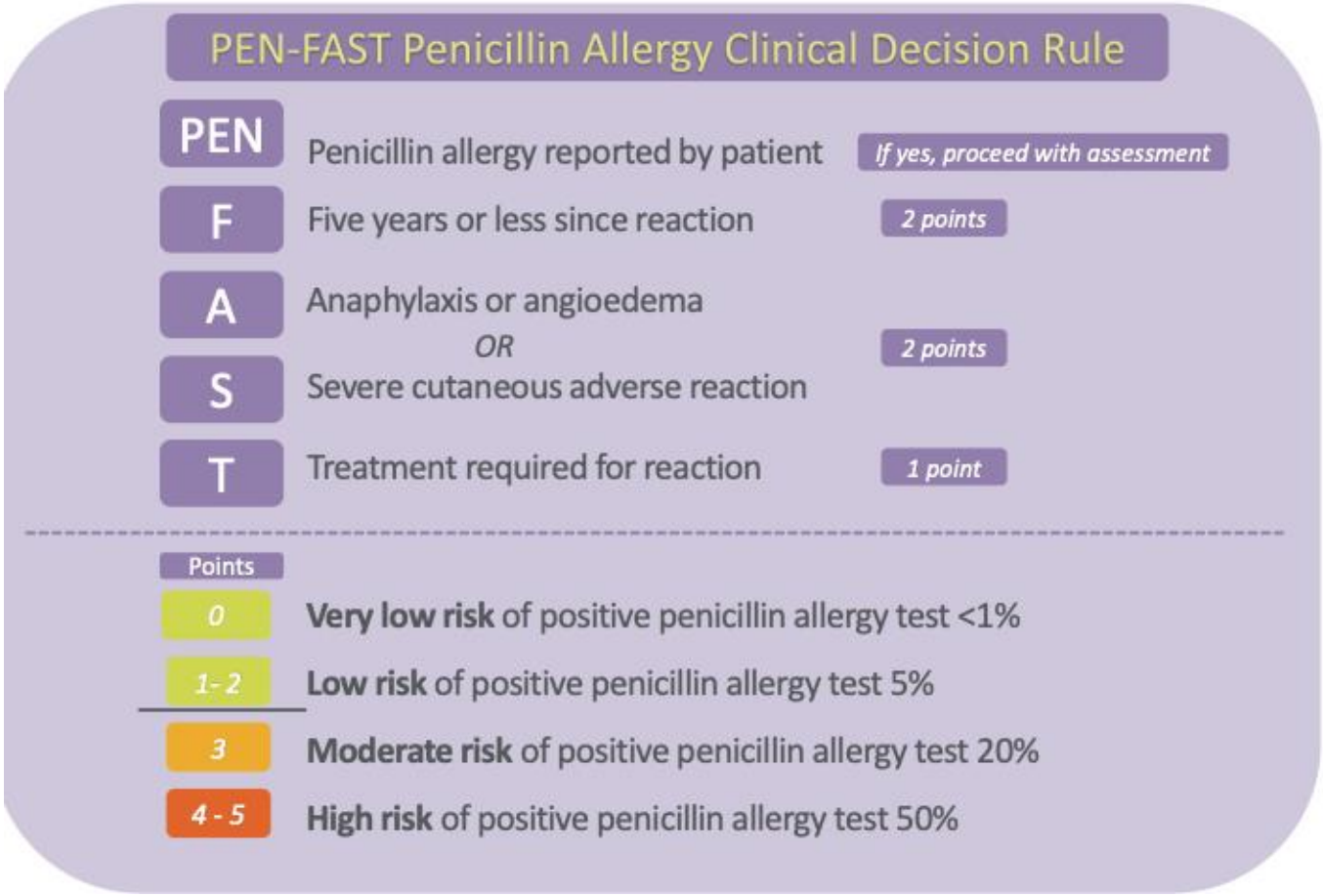
Optimize antibiotic therapy to minimize the risk of *C. diff* infection:

- **Prescribe the most targeted and safe antibiotic.**
  - In patients with a history of *C. diff* infection, avoid the use of higher-risk antibiotics when other effective therapy is available.
  - If a penicillin allergy is listed in the medical record, determine whether your patient is truly allergic to decrease unnecessary use of higher-risk antibiotics.
- **Use the shortest effective antibiotic duration.**
- **Reassess antibiotic therapy based on your patient's clinical condition and relevant culture results.**[1]

Clostridioides difficile (C. diff) **is estimated to cause almost half a million infections in the United States each year.**

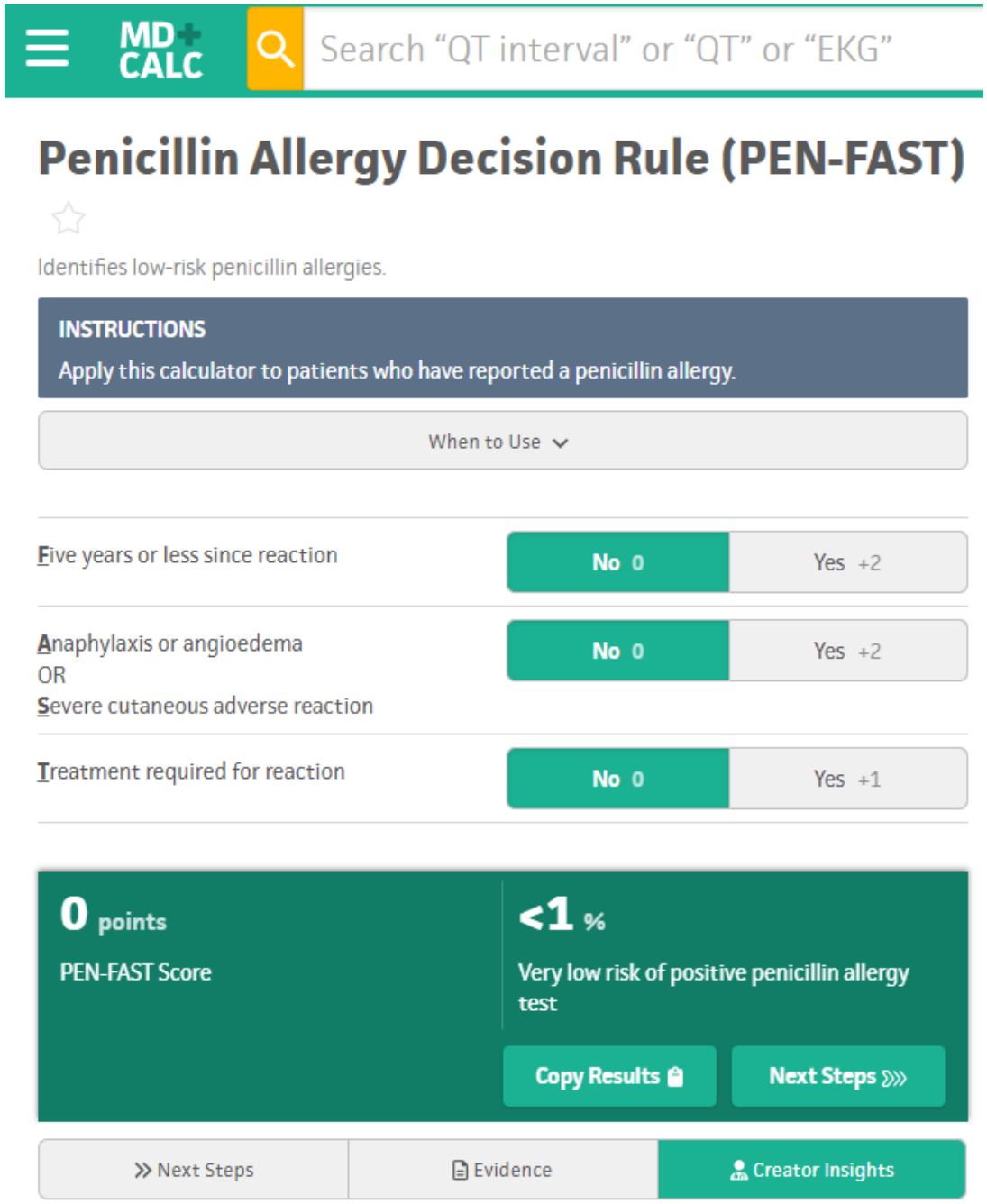
HEALTHCARE PROFESSIONALS: BE ANTIBIOTICS AWARE. C. DIFF INFECTION – IS YOUR PATIENT AT RISK? (cdc.gov)

PEN-FAST Tool to Identify Low-Risk Penicillin Allergies



Negative Predictive Value of Score <3: 96.3%

Trubiano JA, Vogrin S, Chua KYL et al. Development and Validation of a Penicillin Allergy Clinical Decision Rule. JAMA Internal Med. JAMA Intern Med 2020;180[5]:745-752



[Penicillin Allergy Decision Rule (PEN-FAST) (mdcalc.com)]

JAMA Internal Medicine

RCT: Efficacy of a Clinical Decision Rule to Enable Direct Oral Challenge in Patients With Low-Risk Penicillin Allergy

POPULATION

130 Men, 247 Women

Adults ≥18 y old with a low-risk penicillin allergy

Median age, 51 y

INTERVENTION

377 Participants analyzed

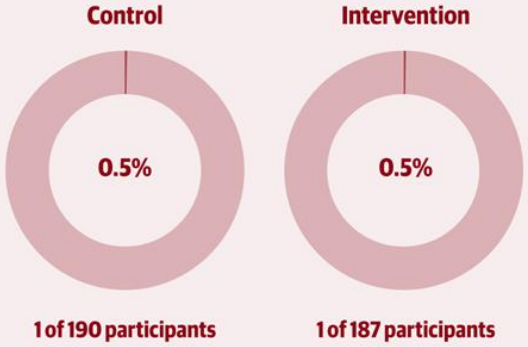
190 Control
Skin prick and intradermal penicillin testing, followed by oral challenge if skin testing results are negative

187 Intervention
Direct oral penicillin drug challenge

FINDINGS

The intervention was found to be noninferior to the control for the primary outcome in adults with low-risk penicillin allergy

Proportion of participants with a positive oral penicillin challenge



Risk difference, 0.0084 (90% CI, -1.22 to 1.24) percentage points, which is less than the noninferiority margin

SETTINGS / LOCATIONS

6 Hospitals in North America and Australia

PRIMARY OUTCOME

Between-group difference in the proportion of participants with a physician-verified immune-mediated positive oral penicillin challenge (percentage points); noninferiority margin was set at 5 percentage points

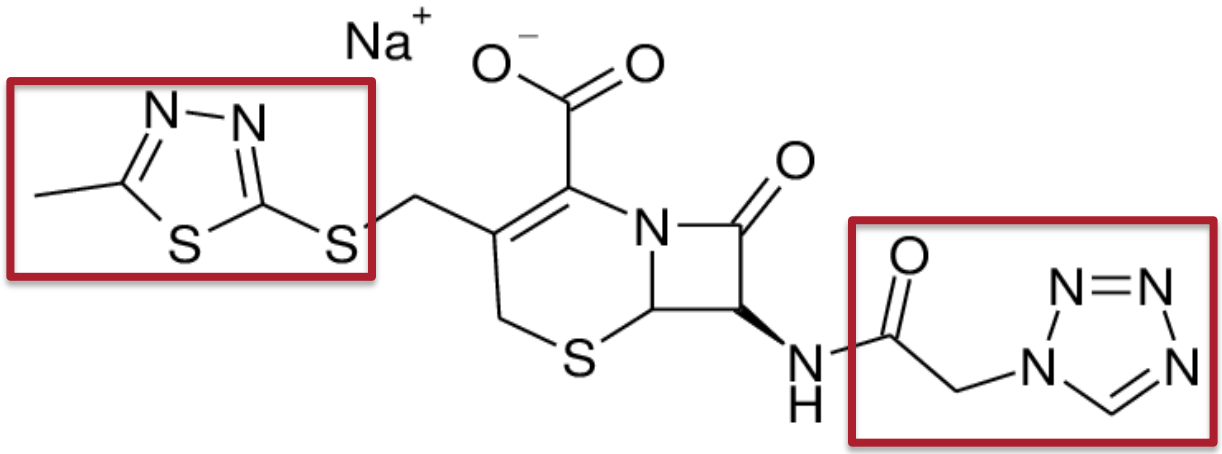
Copaescu AM, Vogrin S, James F, et al. Efficacy of a clinical decision rule to enable direct oral challenge in patients with low-risk penicillin allergy: the PALACE randomized clinical trial. *JAMA Intern Med*. Published online July 17, 2023. doi:10.1001/jamainternmed.2023.2986

- ✓ Low risk patients (PEN-FAST <3) can be administered oral penicillin challenge safely
- ✓ Removes need for specialized allergist assessment

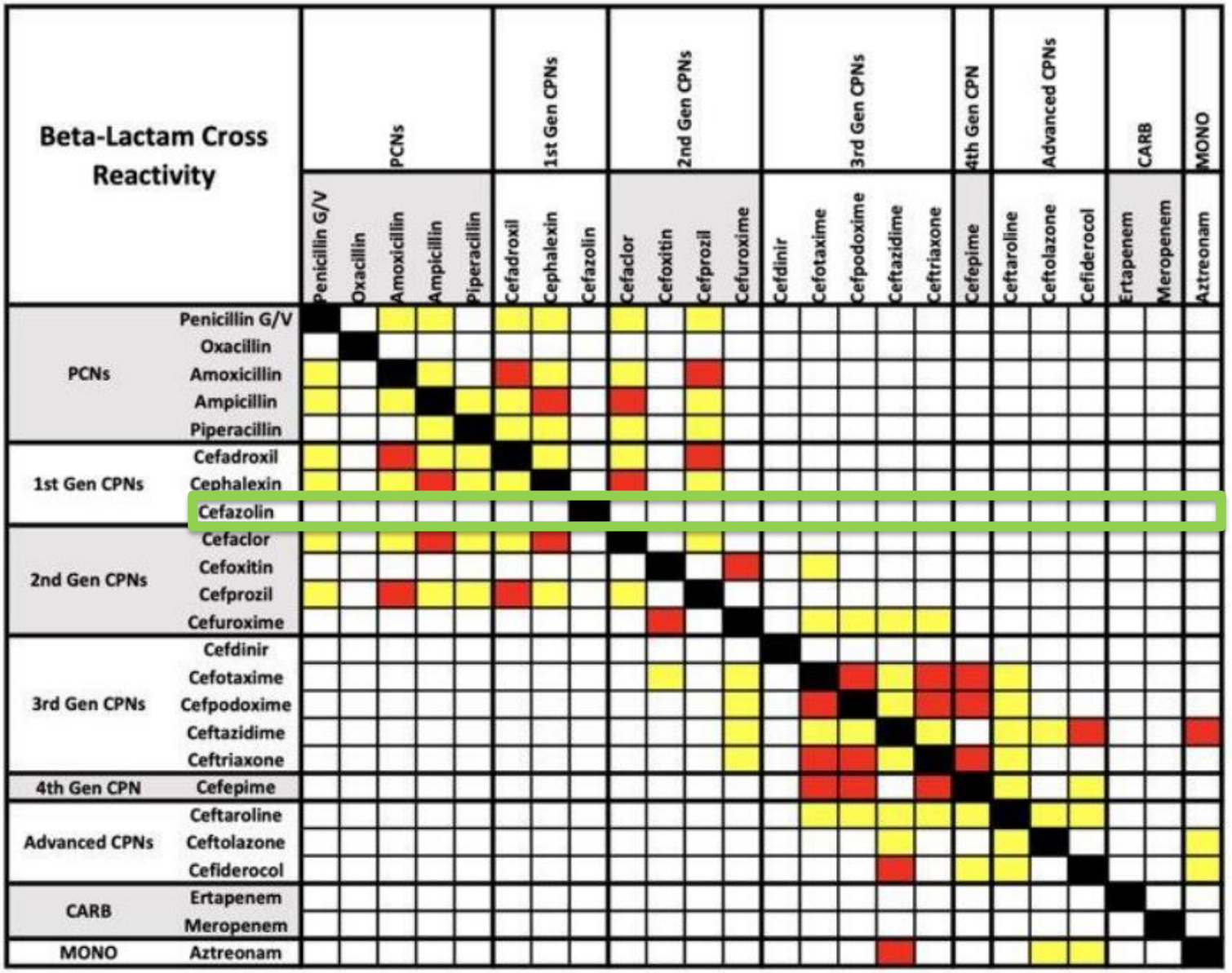
ASAP

Surgical Prophylaxis

- Cefazolin is commonly avoided in patients with penicillin allergy labels (PALs) since historical references quote cross-reactivity rates of 5%–10% between penicillin allergies and reactions to first-generation cephalosporins
- Alternative antibiotics such as **clindamycin** or vancomycin are commonly used for surgical prophylaxis in patients with PALs
- Cefazolin does not share a side chain with any other β-lactam antibiotic and the likelihood of cefazolin allergy in a patient with reported penicillin allergy is ***extremely rare***



Cooper, J. et al. Safety of cefazolin for perioperative prophylaxis in patients with penicillin allergy labels. Annuls of Allergy, Asthma, & Immunology. 2022.



betalactam_crossreactivity.pdf (unmc.edu)

Surgical Prophylaxis

- Meta-analysis of 77 studies
- 44/6147 (0.7%) of patients had a dual allergy with both penicillin and cefazolin
- *The low frequency of penicillin-cefazolin dual allergy suggests that most patients should receive cefazolin regardless of penicillin allergy history.*

Zagursky RJ, Pichichero ME. Cross-reactivity in β-Lactam Allergy. The Journal of Allergy and Clinical Immunology: In Practice. 2018;6(1):72–81.e1.

- Norvell et al described use of cefazolin or clindamycin and/or vancomycin as surgical prophylaxis in patients with reported penicillin allergies.
  - There were fewer SSIs (0.9% vs 3.8%; P < .001), including prosthetic joints infections (0.1% vs 1.9%), among cefazolin-treated patients.
  - More interoperative hypersensitivity reactions occurred in patients receiving clindamycin and/or vancomycin compared to cefazolin (1.3% vs 0.2%)

Norvell MR, Porter M, Ricco MH, Koonce RC, Hogan CA, Basler E, Wong M, Jeffres MN. Cefazolin vs Second-line Antibiotics for Surgical Site Infection Prevention After Total Joint Arthroplasty Among Patients With a Beta-lactam Allergy. Open Forum Infect Dis. 2023 Apr

Perioperative Cefazolin Prescribing Rates Following Suppression of Alerts for non-IgE Mediated Penicillin Allergies

University of Nebraska Medical Center
Nebraska Medicine

Ashley Bogus, PharmD[1]; Kelley McGinnis, PharmD, MS, BCPS[1]; Joshua Vergin[2]; Sara May, MD, FAAAAI[2]; Richard Hankins, MD[2]; Erica Stohs, MD[2]; Trevor C. Van Schooneveld, MD, FACP, FSHEA[2]; Scott J. Bergman, PharmD, FCCP, FIDSA, BCIDP[1,2]
[1]Department of Pharmaceutical and Nutrition Care, Nebraska Medicine, Omaha, NE | [2]University of Nebraska Medical Center, Omaha, NE

#581 SHEA 2023 Seattle, WA

Correspondence:
Ashley Bogus, PharmD
PGY1 Pharmacy Resident
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Background

- Cefazolin is the preferred antimicrobial for the prevention of surgical site infections (SSI)
- Penicillin (PCN) allergies can increase prescribing rates of vancomycin despite low risk of cross-reactivity with cephalosporins

Study Objective

Evaluate changes in perioperative antimicrobial surgical site infection (SSI) prophylaxis following the suppression of alerts for non-IgE-mediated or non-severe penicillin allergies in patients prescribed cephalosporins

Methods

Design: Single-center, quasi-experimental study conducted at a 718-bed academic medical center

- Allergy alert on cephalosporin orders suppressed for all reactions to PCN except: hives, wheals, urticaria, angioedema, "throat swelling," shortness of breath, "trouble breathing," anaphylaxis, SJS, TENS, DRESS

Pre-intervention	Alert Suppressed	Post-intervention
4/1/21-3/31/22	4/11/22	4/11/22-10/31/22

- Education about alert suppression communicated via email to pharmacists and surgical staff

Primary Outcome: Administration of perioperative cefazolin in patients with reported penicillin allergies for procedures where it is preferred for SSI prophylaxis

- For quality improvement, we evaluated safety outcomes for the top surgical procedures starting with <50% cefazolin use in individuals with PCN allergies

Secondary Outcomes:

- Vancomycin prescribing rates
- Incidence of IgE-mediated and severe allergic reaction, rescue medication use, SSI, acute kidney injury, post-op *C. difficile*, and new MRSA infections

Statistical Analysis: Descriptive statistics, Chi-square, Fisher's exact test

Inclusion Criteria

- Age ≥19 years
- Received antibiotics with "surgical prophylaxis" as the indication
- Hospital length of stay ≥ 24 hours

Exclusion Criteria

- Received both IV vancomycin and cefazolin
- Subsequent procedures in the same admission

Results

Figure 1. Patient cohorts

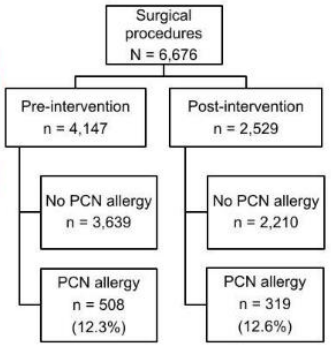
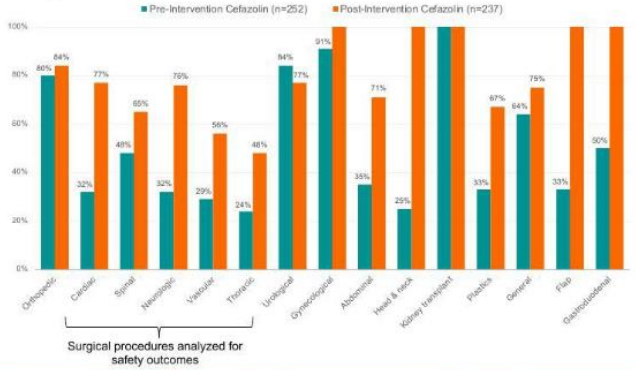


Figure 2. Perioperative cefazolin administration by procedure type, in order of most procedures performed, for patients with PCN allergies



Analysis of Cardiac, Spinal, Neurologic, Vascular, and Thoracic Procedures

Table 1. Baseline Characteristics of Sample, n = 478

Variable	Pre-intervention n = 303	Post-intervention n = 175
Age (years), mean ± SD	61.5 ± 15.6	61.8 ± 15.2
Female	181 (59.7)	104 (59.4)
Non-penicillin beta-lactam allergy	41 (13.5)	21 (12.0)
Prior unknown reaction	41 (13.5)	41 (23.4)
Prior IgE-mediated or severe reaction	116 (38.2)	48 (27.4)
Hives, wheals, urticaria	77 (25.4)	35 (20.0)
Angioedema, "throat swelling"	9 (3.0)	5 (2.9)
Short of breath, "trouble breathing"	10 (3.3)	2 (1.1)
Anaphylaxis	19 (6.3)	6 (3.4)
SJS, TENS, DRESS	1 (0.3)	0 (0)
Prior non-severe reaction	148 (48.8)	82 (46.9)
Rash	76 (25.1)	53 (30.3)
Itching	8 (2.6)	0 (0)
GI symptoms	41 (13.5)	21 (12)
Altered mental status	4 (1.3)	3 (1.7)
Musculoskeletal symptoms	8 (2.6)	3 (1.7)
Other	11 (3.6)	2 (1.1)

Unless otherwise noted all values expressed as no. (%)

Table 2. Outcomes of Sample, n = 478

Variable	Pre-intervention n = 303	Post-intervention n = 175	*p*-value
Cefazolin	105 (34.7)	117 (68.9)	<0.01
Vancomycin	198 (65.3)	58 (33.1)	<0.01
Safety Outcomes			
New severe reaction	2 (0.66)	1 (0.57)	0.90
With cefazolin	0 (0)	1 (0.57)	0.30
With vancomycin	2 (0.7)	0 (0)	0.48
Rescue medication use	4 (1.3)	1 (0.6)	0.66
Epinephrine	0 (0)	0 (0)	n/a
Diphenhydramine	4 (1.3)	1 (0.6)	0.44
Steroids	2 (0.7)	0 (0)	0.28
Surgical site infection	5 (1.7)	3 (1.7)	0.96
Acute kidney injury	32 (10.6)	13 (7.4)	0.26
C. difficile post-op	5 (1.7)	1 (0.6)	0.42
New MRSA infection	5 (1.7)	1 (0.6)	0.52

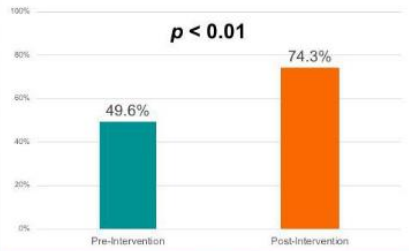
Unless otherwise noted all values expressed as no. (%)

Disclosures

The authors of this presentation have nothing to disclose related to the content of this presentation.

Results

Figure 3. Perioperative cefazolin administration in all patients with PCN allergies when it was preferred agent



Discussion

- In patients with PCN allergies undergoing procedures where cefazolin was the preferred agent, overall cefazolin prescribing significantly improved following the intervention
  - In all individuals, regardless of allergy status, cefazolin prescribing for perioperative SSI prophylaxis was also significantly improved
- Largest change in cefazolin prescribing occurred in PCN allergic patients undergoing cardiac, spinal, neurologic, vascular, and thoracic procedures (Figure 2)
- Patients with unknown history of PCN allergies were included in the EMR alert suppression
- Minimal education required prior to alert suppression
- Rate of severe allergic reactions and use of rescue medications remained low in both cohorts

Limitations

- Single institution study
- Reliance on EHR to capture data
- Short length of follow-up for post-intervention cohort

Conclusions

Prescribing rates of cefazolin for surgical infection prophylaxis significantly improved for procedures where it was the preferred agent following the suppression of EMR alerts for non-IgE mediated and non-severe allergies to penicillins.

ASAP

Perioperative cefazolin prescribing rates following suppression of alerts for non-IgE-mediated penicillin allergies | Antimicrobial Stewardship & Healthcare Epidemiology | Cambridge Core

Perioperative Cefazolin Prescribing Rates following Suppression of EHR Alerts for non-IgE mediated Penicillin Allergies – A Nebraska Medicine Study, 2023

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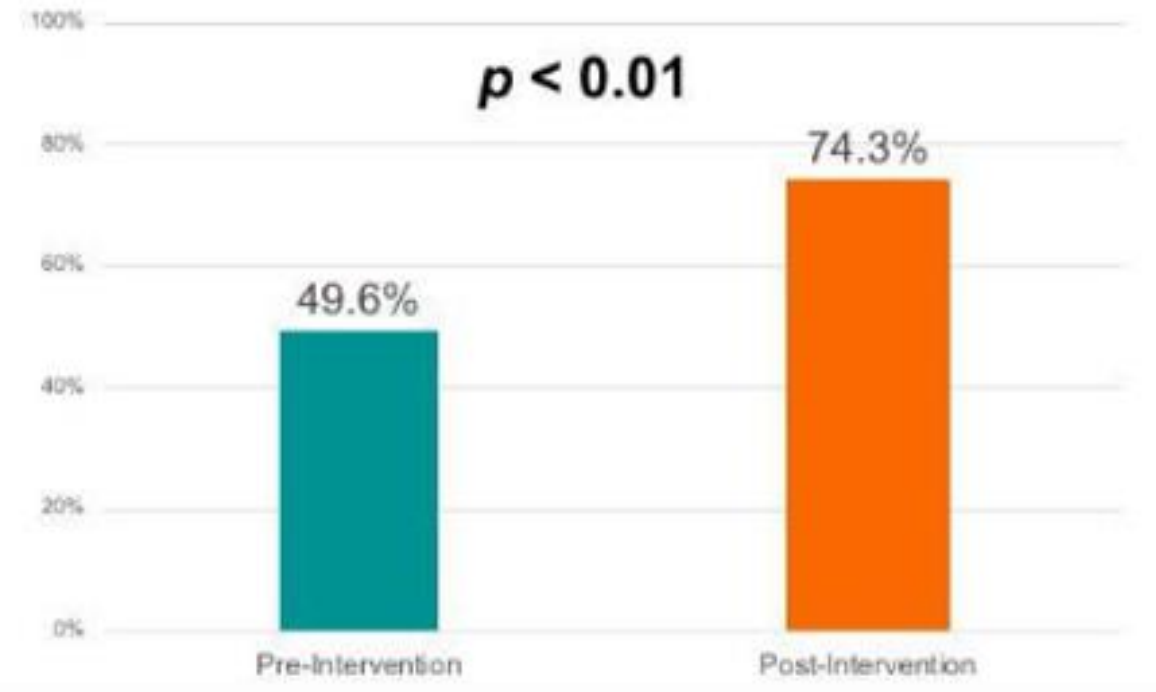

Perioperative cefazolin prescribing rates following suppression of alerts for non-IgE-mediated penicillin allergies | Antimicrobial Stewardship & Healthcare Epidemiology | Cambridge Core

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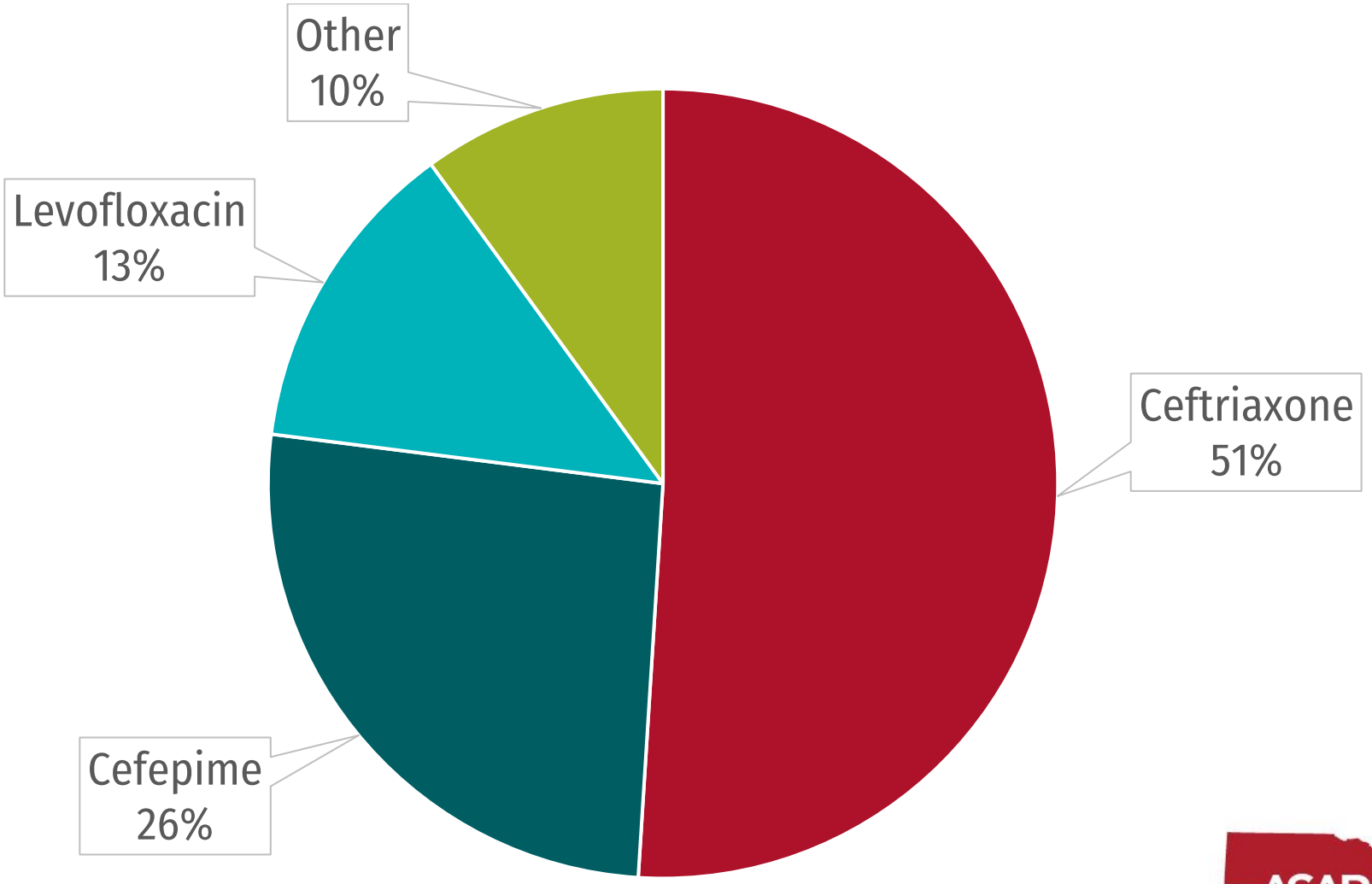
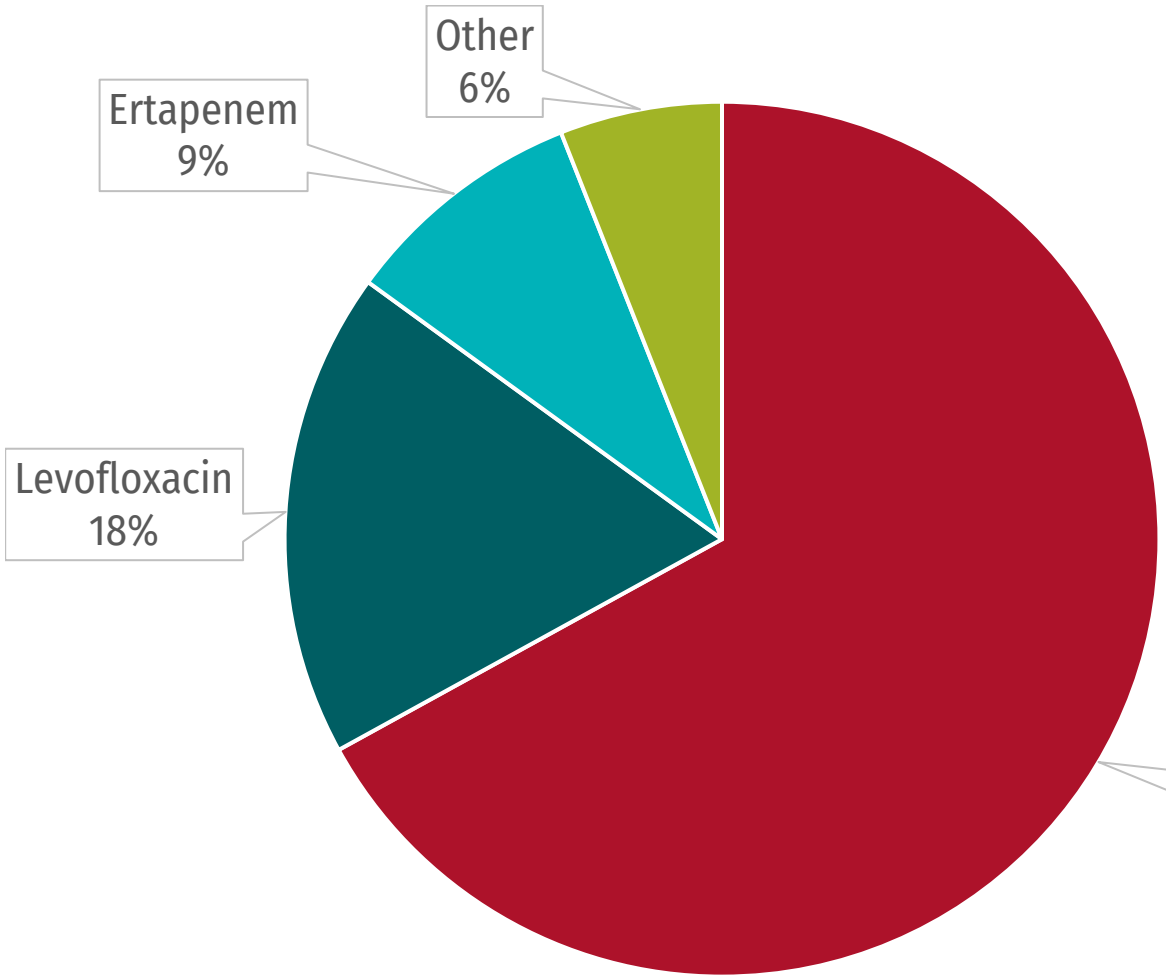
High-Risk CDI Agents in Community-Acquired Pneumonia

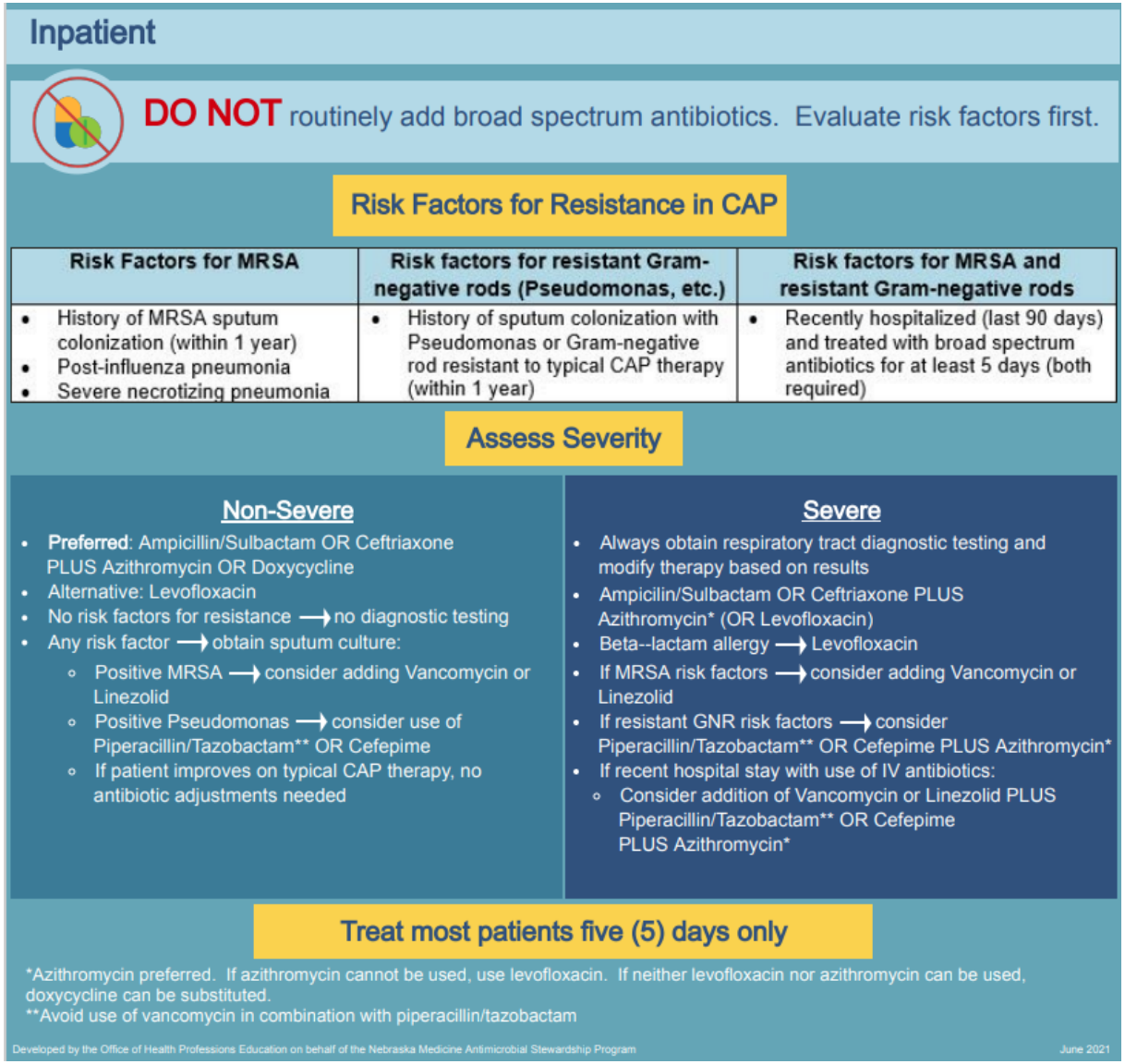
Nebraska NHSN Antibiotic Use Data
High-Risk CDI Agents, 2022-2023



Nebraska NHSN Antibiotic Use Data
Broad-Spectrum Community-Acquired Conditions, 2022-2023



Community-Acquired Pneumonia



Inpatient

DO NOT routinely add broad spectrum antibiotics. Evaluate risk factors first.

Risk Factors for Resistance in CAP

Risk Factors for MRSA	Risk factors for resistant Gram-negative rods (Pseudomonas, etc.)	Risk factors for MRSA and resistant Gram-negative rods
• History of MRSA sputum colonization (within 1 year) • Post-influenza pneumonia • Severe necrotizing pneumonia	• History of sputum colonization with Pseudomonas or Gram-negative rod resistant to typical CAP therapy (within 1 year)	• Recently hospitalized (last 90 days) and treated with broad spectrum antibiotics for at least 5 days (both required)

Assess Severity

Non-Severe

- **Preferred**: Ampicillin/Sulbactam OR Ceftriaxone PLUS Azithromycin OR Doxycycline
- Alternative: Levofloxacin
- No risk factors for resistance → no diagnostic testing
- Any risk factor → obtain sputum culture:
  - Positive MRSA → consider adding Vancomycin or Linezolid
  - Positive Pseudomonas → consider use of Piperacillin/Tazobactam** OR Cefepime
  - If patient improves on typical CAP therapy, no antibiotic adjustments needed

Severe

- Always obtain respiratory tract diagnostic testing and modify therapy based on results
- Ampicilin/Sulbactam OR Ceftriaxone PLUS Azithromycin* (OR Levofloxacin)
- Beta--lactam allergy → Levofloxacin
- If MRSA risk factors → consider adding Vancomycin or Linezolid
- If resistant GNR risk factors → consider Piperacillin/Tazobactam** OR Cefepime PLUS Azithromycin*
- If recent hospital stay with use of IV antibiotics:
  - Consider addition of Vancomycin or Linezolid PLUS Piperacillin/Tazobactam** OR Cefepime PLUS Azithromycin*

Treat most patients five (5) days only

*Azithromycin preferred. If azithromycin cannot be used, use levofloxacin. If neither levofloxacin nor azithromycin can be used, doxycycline can be substituted.
**Avoid use of vancomycin in combination with piperacillin/tazobactam

Developed by the Office of Health Professions Education on behalf of the Nebraska Medicine Antimicrobial Stewardship Program June 2021

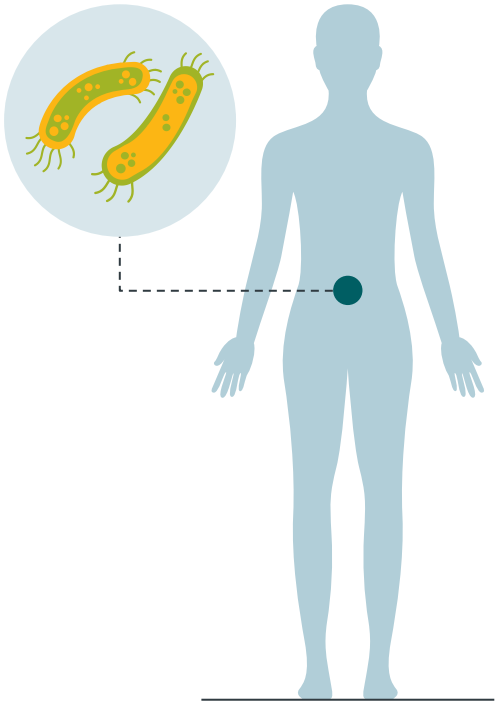
Management of Community Acquired Pneumonia (unmc.edu)

Pharmacy-Driven IV to PO Protocol

- Patient is improving clinically
- Tolerating food or enteral feeding, oral medications
- Able to adequately absorb oral medications via the oral, gastric tube, or nasogastric tube route
- Not displaying signs of shock, not on vasopressor blood pressure support
- Afebrile for at least 24 hours (temperature ≤100.9°F or ≤38.3°C)
- Patient has completed at least 24 hours of intravenous antimicrobial therapy
- Signs and symptoms of infection improvement according to assessment:
  - Improving WBC (decrease of > 2 K/uL + WBC between 4 – 20 K/uL) and/or improving differential counts
  - Improving signs and symptoms
  - Hemodynamically stable: patient is not septic

Ceftriaxone → PO Amoxicillin/clavulanate

SHC-IV-to-PO-Interchange-Protocol.pdf (stanford.edu)



Objective 4

Summarize the role of gastric acid suppression on *Clostridioides difficile* infection risk

Gastric Acid Suppression

- Gastric acid can act as a chemical barrier to prevent proliferation of *C. difficile* spores
- ↓ gastric acid = possible ↑ in CDI risk
- Likely related to the degree of acid suppression
- Proton pump inhibitors (PPIs) > H2 receptor antagonists

https://asap.nebraskamed.com/guidance-for-the-use-of-proton-pump-inhibitors/

May 10, 2010

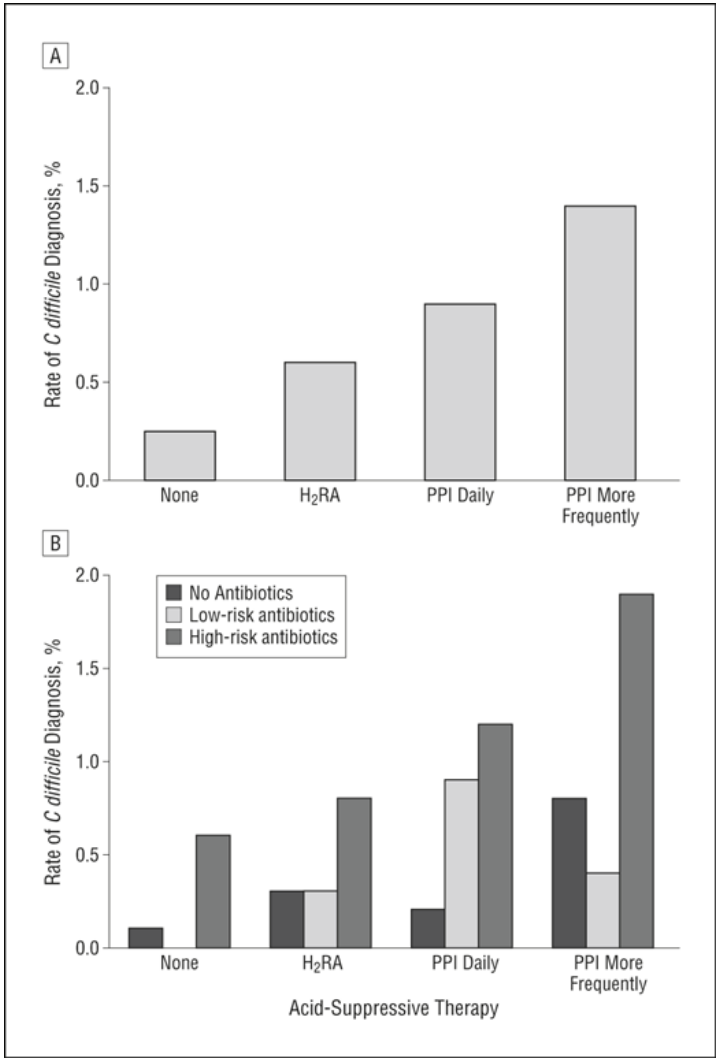
Iatrogenic Gastric Acid Suppression and the Risk of Nosocomial Clostridium difficile Infection

Michael D. Howell, MD, MPH; Victor Novack, MD, PhD; Philip Grgurich, PharmD; et al

Table 2. Multivariable Analysis for Factors Associated With Nosocomial *Clostridium difficile* Infection[a]

Factor	Odds Ratio (95% Confidence Interval)	*P* Value
Acid suppression		
No acid suppression therapy	1 [Reference]	
H_2RA only	1.53 (1.12-2.10)	.008
Daily PPI	1.74 (1.39-2.18)	<.001
PPI more frequently than daily	2.36 (1.79-3.11)	<.001
Age, per year	1.01 (1.01-1.01)	<.001
No antibiotics therapy	1 [Reference]	
Low-risk antibiotics	1.82 (1.17-2.82)	.008
High-risk antibiotics	3.37 (2.64-4.31)	<.001
Weight loss	2.29 (1.57-3.36)	<.001
Chronic heart failure	1.31 (1.06-1.62)	.01
Renal failure	1.57 (1.29-1.91)	<.001
Fluid and electrolyte disorders	1.49 (1.25-1.77)	<.001
Coagulation disorder	1.76 (1.30-2.40)	<.001
Malignancy	1.57 (1.29-1.91)	<.001

Abbreviations: H_2RA, H_2-receptor antagonist; PPI, proton pump inhibitor.
[a] General estimating equation model with diagnosis of nosocomial *C difficile* infection as a dependent variable, controlling simultaneously for variables listed as well as propensity score–based probability of receiving acid-suppressive therapy.



Proton Pump Inhibitor Guidance

- Ensure PPI has an appropriate indication
- If started for prophylaxis, ensure discontinuation at discharge
- Limit dose and duration
- Use H2 receptor antagonist if able

PPI's are indicated for the **treatment** of the following conditions:

- Zollinger-Ellison Syndrome
- Barrett's esophagus
- Acute upper GI bleed
- Erosive esophagitis
- *Helicobacter pylori* treatment
- Gastric or duodenal ulcer
- Gastroesophageal reflux disease (GERD)

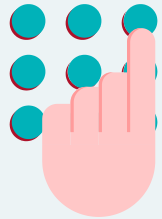
PPI's are considered appropriate for the **prophylaxis** of upper gastrointestinal bleed (UGIB) in the following conditions:

- Mechanical ventilation for greater than 48 hours
- Coagulopathy defined as platelet count <50,000/μL, INR >1.5, or PTT 2x control
- Traumatic head injuries with a Glasgow Coma Score ≤10 or inability to follow simple commands
- Burns affecting >35% of total body surface area
- Major trauma with an Injury Severity Score ≥16
- Spinal cord injury
- Partial hepatectomy
- Solid organ transplantation perioperatively in the ICU setting
- Antiplatelet therapy (usually aspirin + clopidogrel, prasugrel, or ticagrelor) in patients at high risk for GI bleeding (prior history of GI bleeding; age >60 years; concurrent use of anticoagulants, corticosteroids, or NSAID; *Helicobacter pylori* infection)
- Long-term NSAID use in patients with moderate to high risk of GI bleeding
  - Moderate risk is defined as 1 or 2 of the following risks: age >65 years; high dose NSAID therapy (ibuprofen >2400 mg daily, naproxen >1000 mg daily, meloxicam >7.5 mg daily); previous history of uncomplicated ulcer; concurrent use of aspirin, corticosteroids, or anticoagulants)
  - High risk is defined as history of complicated ulcer especially recent, or >2 risk factors outlined in the moderate risk group
- Any 2 of the following
  - Sepsis
  - ICU stay > 7 days
  - Occult bleeding lasting more than 6 days
  - High dose corticosteroids (> 250 mg/day of hydrocortisone, >50 mg/day of methylprednisolone, >60 mg/day of prednisone, >10 mg/day of dexamethasone)

https://asap.nebraskamed.com/guidance-for-the-use-of-proton-pump-inhibitors/

Summary

01



The highest-risk antibiotics for *C. diff* infection include:

- ❑ Clindamycin
- ❑ Fluoroquinolones
- ❑ Carbapenems
- ❑ 3rd/4th generation cephalosporins

02

Proton pump inhibitors decrease gastric acid production, thereby also increasing risk of CDI.

03

Stewardship interventions centered around these agents can have large impacts on CDI rates – **action is key**

Questions?

Jenna Preusker, PharmD, BCPS, BCIDP

Nebraska ASAP Pharmacy Coordinator

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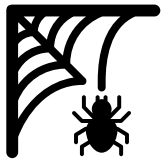

ASAP